EXHIBIT 1

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Aging and the Cardiovascular System

Samer S. Najjar, Gary Gerstenblith, and Edward G. Lakatta

Key Points

- Cardiovascular aging is characterized by increased thickness and stiffness of the central arterial walls, a preserved ejection fraction at rest through an increase in the thickness of the left ventricular wall, an enhanced ability of the myocardium to bear force in late systole, and diminished responsiveness to β-adrenergic modulation.
- During maximal exercise older individuals, as compared to younger individuals, exhibit diminished exercise capacity with preserved cardiac reserve, due to peripheral factors that determine oxygen utilization, lower ejection fraction due to an age-associated uncoupling of arterial and cardiac energies, and reduced cardiac output with preserved stroke volume, due to an age-associated decrease in maximal heart rate.
- The incidence and prevalence of cardiovascular diseases increase with advancing age. This association may be explained, in part, by the fact that many of the same factors that underlie the age-associated structural and functional alterations in central arterial walls are also implicated in the pathogenesis of cardiovascular diseases.

Overall cardiovascular function varies dramatically among elderly individuals. This is due in part to a sharp increase in the prevalence of coronary disease (both overt and occult) with advancing age and in part to major age-associated changes in lifestyle (e.g., fitness status). Thus, the identification of cardiovascular structural and functional changes that reflect an "aging process" per se is a formidable task; neither functional differences among individuals in cross-sectional studies nor changes with time in a given individual in longitudinal studies are necessarily manifestations of an aging process. Rather, interactions among aging, disease, and lifestyle must be considered in interpreting age-associated changes in cardiovascular structure and function as measured in various studies.[1]

Cardiovascular Changes with Aging

Vascular Structure and Function

Ventricular structure and function are in part regulated by the properties of the vasculature to which the heart is connected, in particular by the peripheral vascular resistance (PVR), arterial impedance, and reflected pulse waves (Fig. 115.1).

Arterial stiffening occurs with aging even in the absence of clinical hypertension (Fig. 115.1).[2] Even in the absence of clinical hypertension, systolic arterial pressure increases and is considered to result from the age-associated increase in arterial stiffness (Fig. 115.1). In populations in whom the increase in arterial stiffness with age is blunted, the arterial pressure increase with age is also blunted. The increased arterial stiffness may not be related strictly to an age-associated change in vascular structure, but may also be due in part to increased arterial tonus. There is evidence that baroreceptor activity decreases with age, and this also has been implicated in the general age-associated increase in arterial pressure. In addition, plasma catecholamines increase with aging,[3] which may be a result of exaggerated central nervous system (CNS) adrenergic flow, possibly associated with blunting of baroreceptor sensitivity. However, elevated plasma catecholamine levels in older individuals are associated with a diminished postsynaptic β-adrenergic response of the heart and vasculature (see below). It is possible that the diminished postsynaptic response itself could be secondary to exaggerated receptor stimulation and related, in part, to a deficient baroreflex, which leads to inappropriate CNS sympathetic flow. Plasma catecholamine levels, however, are not correlated or are inversely correlated with arterial pressure in elderly normotensives and hypertensives.

A modest increase in PVR accompanies aging in some but not all individuals, and when it does occur it may, in part, be secondary to a reduction in skeletal muscle-mass,[4,5]

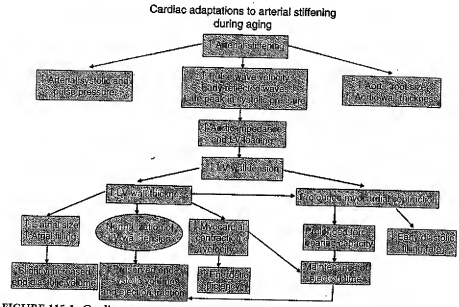

FIGURE 115.1. Cardiac consequences of age-associated increase in central arterial stiffness.

with a concomitant reduction in capillary density. The PVR is also commonly found to be moderately increased in those older individuals with predominantly systolic hypertension. A selective increase in renal arterial resistance occurs with aging and is not secondary to reduced cardiac output.[6] The nature of this increase in renal vascular resistance is not fully understood, but it causes the renal blood flow per gram of kidney weight to decrease progressively after the fourth decade.

Arterial stiffness is a major determinant of arterial impedance, which affects the pulsatile ejection of blood from the heart.[7] The aortic impedance is composed of many frequency components. The zero frequency impedance modulus is the PVR, as noted above. The average of the higher frequency impedance moduli, referred to as the characteristic aortic impedance, is the opposition to pulsatile flow. Abnormalities in aortic distensibility, such as those associated with advancing age and clinical hypertension, create a mismatch between ventricular ejection and aortic flow energies, causing the characteristic aortic impedance modulus to increase with age.[7] The increased pulse wave velocity, resulting from increased vascular stiffness, is one cause of early wave reflection from peripheral sites to reach the ascending aorta during the ventricular ejection period (Fig. 115.1). This causes aortic and carotid pressures to continue to increase to a later time during ejection, resulting in an increase in central systolic and pulse pressures and a change in the aortic pressure pulse contour of these arteries, which includes a late-occurring peak, and a reduction in diastolic blood pressure, which has the potential to compromise coronary filling.[7] Pulse wave reflection, in addition to elevating aortic pressure, imposes an additional component to the total vascular load on the left ventricle (LV).[7] Therefore, the total arterial load placed on the LV can be characterized by PVR, characteristic aortic impedance, and pulse wave reflection. An increase in intimal-medial thickness accompanies the age-associated increase in arterial stiffness.[1]

A host of cellular and molecular mechanisms that underlie arterial intimal medial thickening and stiffening with advancing age have been identified.[8] These include elevated levels or activity of molecules such as matrix metalloproteinase-2 (MMP-2), angiotensin II [Ang-II], transforming growth factor-β (TGF-β), the chemoattractant platelet-derived growth factor (PDGF), monocyte chemoattractant protein-1 (MCP-1), interstitial cell adhesion molecule-1 (ICAM-1), and reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Each of these factors is a signaling target downstream of the angiotensin AT1 receptor. Ang-II increases MMP-2 activity in the aged arterial wall, and increases transcription of TGF-β and the TGF-β II receptor. Activated MMP-2 activates TGF-β, leading to enhanced transcription of fibronectin and collagen genes. Ang-II signaling also increases the production of MCP-1 and its receptor, CCR-2, in arterial endothelial and vascular smooth muscle cells. Another sign of increased inflammation is enhanced NADPH oxidase activity, which also results, in part, from an age-associated increase in arterial Ang-II signaling. Excessive NADPH oxidase produces superoxide, which reacts with nitric oxide to produce the toxic species, peroxynitrite, which can lead to protein nitration, and "steals" nitric oxide in the process, reducing its bioavailability. This may explain, in part, the endothelial dysfunction that is observed in older ages.[9,10]

Interactions among these factors create a metabolically active environment.[11–13] Some vascular smooth muscle cells (VSMC) shift their phenotype from contractile to secretory, proliferative, and invasive, and migrate into the thickened intima. Enhanced VSMC invasion of the matrix within the older arterial wall is promoted by activation of MMP-2, by elaboration of PDGF-β and its receptor, and by MCP-1 and its receptor, CCR-2. Arterial wall elastin becomes fragmented with advancing age, and excessive collagen is synthesized and becomes nonenzymatically glycated. Endothelial dysfunction and its attendant alterations in endothelial permeability and vasotonic actions occur.

These same metabolic, enzymatic, cellular, and endothelial alterations appear to play a critical role in the genesis or promotion of hypertension, atherosclerosis, vascular inflammation, vascular remodeling, and oxidant stress. Many of the same factors that underlie the age-associated structural and functional alterations of the arterial intima and media are also implicated in the pathogenesis of clinical arterial diseases.[11]

Another important factor associated with vascular aging may be a decrease in the elaboration or function of endothelial progenitor cells.[14] Recent research indicates that following injury; endogenous progenitor cells may participate in repair and replacement processes.[15] Endothelial progenitor cells (EPCs) are one type of progenitor cells and are believed to stimulate the formation of entirely new blood vessels, vasculogenesis, as well as growth of existing vessels or angiogenesis,[16] which is impaired with aging.[17] The EPCs may also transdifferentiate to form myocyte precursors.[18] Animal studies indicate that EPC number and probably function are also decreased with age, and that it might be possible to reverse this decline.[19,20] The effect of such interventions in patients with disease have not been evaluated to date.

Cardiac Structure and Function at Rest

Overall cardiac function in most elderly individuals who do not have clinical or occult disease is adequate to meet the body's pressure or flow requirements at rest. Two cardiac adaptations occur to sustain normal LV ejection in older persons in the presence of the greater arterial afterload (Fig. 115.1). First, the LV wall thickens modestly, largely owing to an increase in myocyte size. The number of myocytes in the older heart may decrease because of dropout of some cells.[21] However, the increase in size of the remaining cells in most but not all instances compensates for the cell loss. An increase in the amount of interstitial collagen also occurs. Second, the ability of the myocardium to bear force in late systole is increased and is manifest as a prolongation of the isovolumic relaxation time (Fig. 115.1); This may be due at least in part to a prolongation of the myofilament Ca^{2+} activation that occurs during systole. Studies in animal models have shown that prolonged contractile activation in the aged heart is accomplished by a prolonged cytosolic free Ca^{2+} transient, partly resulting from a reduction in the rate of Ca^{2+} resequestration by Ca^{2+} sinks within the cell.[22] Although the prolonged contractile activation and possibly structural changes in the heart cause the LV early diastolic filling rate to be reduced in healthy elderly humans, an enhanced atrial contribution to ventricular filling maintains the end-diastolic volume at a normal level in most elderly individuals (Fig. 115.1). In men,[23] a modest cardiac dilatation at end-diastole occurs with aging. The end-systolic volume and ejection fraction at rest are not age-related.[23]

Although ejection fraction (EF) is clinically considered an important index of left ventricular (LV) systolic function, it is not exclusively governed by LV properties. Rather, EF is determined by the interaction of arterial and ventricular properties.[24–26] Effective arterial elastance (Ea) is a steady-state arterial parameter that characterizes the functional properties of the arterial system by incorporating peripheral vascular resistance, total lumped vascular compliance, characteristic impedance, and systolic and diastolic time intervals.[24] Effective arterial elastance can be characterized by the relationship of end systolic pressure and stroke volume, and it shares common units with elastance measures of ventricular function (E_{LV}). E_{LV} is the relationship of end systolic pressure to end systolic volume. The ratio Ea/E_{LV}, an index of arterial-ventricular coupling,[24] is mathematically inversely related to EF.[27] At rest, Ea/E_{LV} does not differ with age in normotensive men or women.[28]

Cardiovascular Function During Exercise

Although there is a decrease in the maximal aerobic work capacity in most healthy older individuals, it has become clear that this limitation may not be due solely to limitations of the central circulation. Rather, the limitations of exercise ability in the aged subject are, at least in part, related to peripheral factors that determine oxygen utilization. Peripheral factors that appear to be involved in the age-associated decline in the maximal oxygen consumption, VO_{2max}, include a decline in skeletal muscle mass with aging.[4,5] Despite this decline, body mass may remain constant because of an increase in body fat, not only subcutaneous but also intraperitoneal and intramuscular.[4,5] When the VO_{2max} is normalized to muscle mass instead of body weight, the magnitude of the decline associated with aging between 25 and 80 years of age decreases from 60% to 14% in men and from 50% to 8% in women.[29] Physical conditioning of older men increases muscle mass and the oxidative capacity per unit of muscle mass.[5]

During high levels of physical exertion, the heart rate is substantially lower in healthy elderly versus younger individuals. The peak rate of LV filling increases in both younger and older subjects during exercise, but a diminished rate of filling of similar magnitude as that observed at rest (i.e., about a 50% reduction) is observed in older individuals during exercise.[30] However, cardiac dilatation at end-diastole and end-systole still occurs during vigorous exercise in older men. This dilatation is more pronounced in elderly individuals who have silent ischemia (i.e., who do not have signs or symptoms of coronary disease at rest but during exercise have an abnormal electrocardiogram [ECG] and an abnormal thallium scan). Therefore, healthy older persons do not exhibit a compromised end-diastolic volume due to a "stiff heart," either at rest or during exercise.[23,31] However, end-diastolic pressure may increase with age. During vigorous exercise the LV stroke volume, which depends on the end-diastolic and end-systolic volumes, is not reduced in healthy elderly subjects. Therefore, in these individuals the cardiac dilatation at end-diastole outweighs the concomitant age-associated deficiency in end-systolic volume reduction. The maximal cardiac index decreases by about 25% with age and is due to a reduced ability for heart rate acceleration to occur.[23] The exercise induced increase in EF is also blunted with advancing age.[23] The failure to increase the LV ejection fraction during exercise is more severe in older persons who have silent ischemia than in those without evidence of coronary disease,[32] and is due to a more pronounced inability to reduce the end-systolic volume.

The blunted increase in EF during exercise (i.e., EF reserve)[23,28] suggests age-associated differences in the shift of

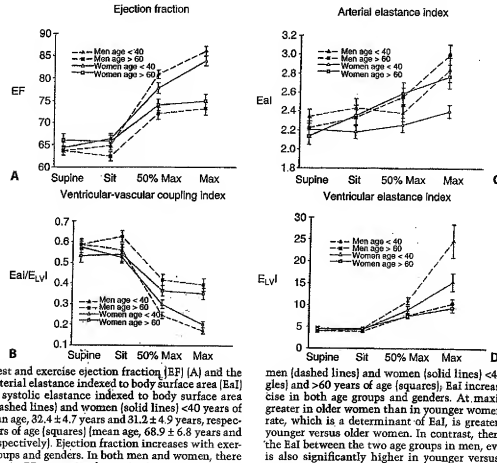

FIGURE 115.2. Rest and exercise ejection fraction [EF] (A) and the ratio of effective arterial elastance indexed to body surface area [EaI] to left ventricular systolic elastance indexed to body surface area [E_{LV}I] (B) in men (dashed lines) and women (solid lines) <40 years of age (triangles) (mean age, 32.4 ± 4.7 years and 31.2 ± 4.9 years, respectively) and >60 years of age (squares) (mean age, 68.9 ± 6.8 years and 70.4 ± 7.1 years, respectively). Ejection fraction increases with exercise in both age groups and genders. In both men and women, there is a greater increase in EF at maximal exercise in younger than in older subjects; EaI/E_{LV}I decreases with exercise in both age groups and genders. In both men and women, there is a greater decrease in EaI/E_{LV}I at maximal exercise in younger than in older subjects ($p \leq .0001$ for men and women). Rest and exercise EaI (C) and E_{LV}I (D) in men (dashed lines) and women (solid lines) <40 years of age (triangles) and >60 years of age (squares). EaI increases from rest to exercise in both age groups and genders. At maximal exercise, EaI is greater in older women than in younger women, even though heart rate, which is a determinant of EaI, is greater at peak exercise in younger versus older women. In contrast, there is no difference in the EaI between the two age groups in men, even though heart rate is also significantly higher in younger versus older men at peak exercise; E_{LV}I increases with exercise in both age groups and genders. At maximal exercise, E_{LV}I is greater in younger men compared with older men and tends to be greater in younger women than in older women.

the arterial-ventricular coupling ratio and its components during exercise. Age-associated differences in Ea/E_{LV} occur in both sexes during exercise (Fig. 115.2). In both sexes, Ea/E_{LV} decreases during exercise (because E_{LV} increases more than Ea), but the ratio declines to a lesser extent in older subjects. There are gender differences in the components of Ea/E_{LV} during exercise: Ea is greater in older versus young women but is unaffected by age in men. E_{LV} increases to a greater extent in young versus older subjects. Thus, suboptimal ventricular-vascular coupling helps to explain the age-associated blunting of maximal exercise EF, and its underlying mechanisms appear to differ between men and women.

β-Adrenergic Modulation of Cardiovascular Performance

The hemodynamic pattern observed in many healthy older persons during exercise [i.e., reduced heart rate and greater cardiac dilatation at end-diastole and end-systole, with maintenance or augmentation of stroke volume] occurs in younger individuals who exercise in the presence of β-adrenergic blockade. Indeed, the age-associated differences in heart rate,[30,33] LV end-diastolic volume, and LV filling rate during exercise are abolished when this exercise is performed during β-adrenergic blockade (Fig. 115.3).

When perspectives from studies that range from measurements of the stress response in intact humans to measurements of subcellular biochemistry in animal models are integrated, a diminished responsiveness to β-adrenergic modulation is among the most notable changes that occur in the cardiovascular system with advancing age [reviewed elsewhere[34]]. β-adrenergic modulation of cardiac pacemaker cells accounts in part for the increase in heart rate during exercise. Bolus infusions of β-adrenergic agonists cause a diminished heart rate response in elderly versus younger subjects.[35] Both the β-adrenergic relaxation of large arteries and the β-adrenergic augmentation of myocardial performance facilitate the ejection of blood from the heart. Therefore, a reduced ability of β-adrenergic stimulation to augment myocardial contractility or to dilate arteries during exercise may be implicated in the alterations in the ventricular ejection pattern observed in some elderly individuals [i.e., a defi-

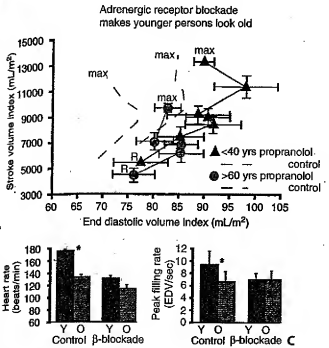

FIGURE 115.3. (A) Stroke volume index (SVI) as a function of end-diastolic volume index (EDVI) at rest (R) and during graded cycle workloads in the upright seated position in healthy men from the Baltimore Longitudinal Study of Aging (25A) in the presence and absence (dashed line) of β-adrenergic blockade. R, seated rest; 1–4 or 5, graded submaximal workloads on cycle ergometer; max, maximum effort. SVI vs. EDVI functions represented by dashed lines without symbols are those measured in the absence of propranolol; the functions with symbols are those measured in the presence of propranolol. Note that in the absence of propranolol the SVI vs. EDVI relation in older persons is shifted rightward from that in younger ones. This indicates that the LV of older persons in the sitting position compared to that of younger ones operates from a greater preload both at rest, during submaximal and maximum exercise. Propranolol markedly shifts the SV-EDV relationship in younger persons (triangles) rightward, but does not markedly affect the curve in older persons (circles). Thus, with respect to this assessment of ventricular function curve, β-adrenergic blockade with propranolol makes younger men appear like older ones. The abolition of the age-associated differences in the LV function curve after propranolol is accompanied by a reduction or abolition of the age-associated reduction in maximum heart rate (B). Note, however, that β-adrenergic blockade in younger individuals (A) causes SVI to increase to a greater extent than during β blockade in older ones, suggesting that mechanisms other than deficient β-adrenergic regulation compromises LV ejection. One potential mechanism is an age-associated decrease in maximum intrinsic myocardial contractility. Another likely mechanism is enhanced vascular afterload, due to the structural changes in compliance arteries noted above, and possibly also to impaired vasorelaxation during exercise. (B) Peak exercise heart rate in the same subjects as in A in the presence and absence of acute β-adrenergic blockade by propranolol. Y, young; O, old. (C) The age-associated reduction in peak LV diastolic filling rate at maximum exercise in healthy BLSA subjects is abolished during exercise in the presence of β-adrenergic blockade with propranolol. Solid bar, <40 years; striped bar, >60 years.[3]

ciency of β-adrenergic action could partially account for the relative failure of end-systolic volume to decrease as much during exercise in older individuals as in younger ones). Age-associated changes in the effectiveness of β-adrenergic stimulation of the myocardium have been demonstrated most extensively in the rat model.[36] In isolated cardiac muscle, perfused myocardium, and cardiac cells from rats of advanced age, β-adrenergic enhancement of the contraction amplitude is diminished compared with that in younger adult rat cardiac tissue or cells.[35] Age-associated reductions in the ability of β-adrenergic stimulation to relax arteries and veins in humans and in isolated aortac muscles from senescent animals have also been demonstrated.[35]

Discussion

Overall cardiovascular function in most older subjects who do not have clinical or occult cardiac disease is adequate to meet the body's requirements for pressure and flow at rest. The basal supine heart rate is unchanged with aging, but systolic and pulse pressures become moderately increased. This pressure increase occurs during late systole and is due, in part, to early pulse wave reflection from the periphery, resulting from an increase in arterial stiffness. Diffuse intimal thickening of central arteries occurs with aging. Although each of these factors changes with age, the extent of change varies dramatically among individuals.

To sustain normal LV ejection, the LV wall thickens modestly, largely because of an increase in myocyte size, and the ability of the myocardium to bear force in late systole is increased, at least in part due to a prolongation of myofilament Ca^{2+} activation. Although prolonged contractile activation and possibly structural changes in the heart cause the LV early diastolic filling rate to be reduced in healthy elderly humans, an enhanced atrial contribution to ventricular filling prevents a reduction in end-diastolic volume, which is actually mildly increased with age. The end-systolic volume and ejection fraction at rest are not age related.

Although aerobic capacity declines with advancing age in individuals without cardiac disease, the extent to which this can be attributed to a decrement in cardiac reserve is not certain. A substantial part of the age-associated decline in maximal oxygen consumption appears to be due to peripheral factors, and, at least in part, can be attributed to an increase in body fat and a decrease in muscle mass with age. Although heart rate is lower in healthy elderly versus younger individuals at high levels of physical work, cardiac dilatation at end-diastole and end-systole occurs in older subjects. Therefore, healthy older subjects do not exhibit a compromised end-diastolic volume due to a "stiff heart," even during exercise. Whereas stroke volume in such individuals is preserved by cardiac dilatation, the increase in ejection fraction with exercise is blunted.

Exercise EF reserve declines with increasing age in both genders and reflects an age-associated uncoupling of cardiac and arterial energies. In women, this is likely due to an age-associated increase in exercise arterial elastance without an appropriate rise in ventricular elastance. In men, this is due to an age-related decline in exercise LV elastance index, as arterial elastance does not change with age. Therapies aimed at improving ventricular-vascular coupling in the elderly may improve exercise performance.

This same hemodynamic pattern (i.e., a reduced exercise heart rate and greater cardiac dilatation at end-diastole and end-systole) occurs in subjects of any age who exercise in the presence of β-adrenergic blockade.

Cardiovascular Aging and Clinical Medicine

In spite of the interest in the physiology of the age-associated changes in cardiovascular structure and function, cardiovascular aging has remained, for the most part, outside of mainstream clinical medicine. This is because the pathophysiologic implications of these changes are largely underappreciated and are not well disseminated in the medical community. In fact, age has traditionally been considered a nonmodifiable risk factor. However, as noted in the preceding sections, many of the age-associated alterations in cardiovascular structure and function, at both the cellular and molecular levels, ought not to be simply considered as part of a normal or physiologic aging process, but rather should be construed as specific risk factors for cardiovascular diseases (Table 115.1). This highlights the urgency to incorporate cardiovascular aging into clinical medicine, which will require that the following steps be implemented.

First, clinicians should be educated regarding those aspects of cardiovascular aging that are risky. This educational process should be geared toward all physicians taking care of middle-aged or older individuals, not just geriatricians, since many of the risky components—often referred to as "subclinical disease"—begin to appear in middle age, which is when they start exerting their toll, and which is when preventive strategies (once they are developed, see below) should be implemented in order to extract the most benefit. Beyond presenting the epidemiologic data implicating the markers of cardiovascular aging as risk factors for disease, the educational curriculum should also include several important concepts that have been discussed in this chapter, which would enable a fuller appreciation of the impact of these risk factors, including the differentiation between successful, usual, and unsuccessful cardiovascular aging, which are in many ways the products of age-disease interactions.

This educational process needs to be complemented by aggressive efforts to set up normative values for each risk marker within a specific population, and adjusted for age groups and gender. This, in turn, is dependent on standardizing the methodologies, techniques, and protocols utilized for acquiring and interpreting these measurements. Findings from the epidemiologic studies can then be incorporated to determine the specific thresholds, or cutoff values, that would distinguish successful (or desired) values, from normal values, from preclinical values, and from disease values.

Concomitantly, aggressive efforts should be undertaken to develop effective therapies to prevent, delay, or attenuate

TABLE 115.1. Relationship of cardiovascular human aging in health to cardiovascular diseases

Age-associated changes	*Plausible mechanisms*	*Possible relation to human disease*
Cardiovascular structural remodeling		
Vascular intimal thickness	Migration of and matrix production by VSMC Possible derivation of intimal cells from other sources	Early stages of atherosclerosis
Vascular stiffness	Elastin fragmentation Elastase activity Collagen production by VSMC Cross-linking of collagen Altered growth factor regulation/tissue repair mechanisms	Systolic hypertension Left ventricular wall thickening Stroke Atherosclerosis
LV wall thickness	LV myocyte size with altered Ca^{2+} handling Myocyte number (necrotic and apoptotic death) Altered growth factor regulation Focal matrix collagen deposition	Retarded early diastolic cardiac filling Cardiac filling pressure Lower threshold for dyspnea Likelihood of heart failure with relatively normal systolic function
Left atrial size	Left atrial pressure/volume	Prevalence of lone atrial fibrillation and other atrial arrhythmias
Cardiovascular functional changes		
Altered regulation of vascular tone	No production/effects	Vascular stiffening; hypertension Early atherosclerosis
Reduced threshold for cell Ca^{2+} overload	Changes in gene expression of proteins that regulate Ca^{2+} handling; increased 6:3 polyunsaturated fatty acids ratio in cardiac membranes	Lower threshold for atrial and ventricular arrhythmia Increased myocyte death Increased fibrosis
Cardiovascular reserve	Vascular load Intrinsic myocardial contractility Plasma levels of catecholamines Adrenergic modulation of heart rate myocardial contractility and vascular tone due to postsynaptic signaling deficits	Reduced diastolic and systolic function Lower threshold for, and increased severity of, heart failure
Reduced physical activity	Learned lifestyle	Exaggerate age associated changes in some aspects of cardiovascular structure and function Negative impact on atherosclerotic vascular disease, hypertension and heart failure

LV, left ventricular; No, nitric oxide; VSMC, vascular smooth muscle cells.

the cardiovascular changes that accompany aging. This is a critical step because if such interventions are not developed in a timely manner, then the recognition of cardiovascular aging as a risk marker for disease would remain an epidemiologic finding of historical interest only. Thus, investigating these preventive measures should be a top research priority, and future efforts will require the close collaboration of a consortium of researchers, including molecular cardiologists, cardiovascular physiologists, and translational clinical trialists.

As progress is made in further elucidating the diverse molecular mechanisms that underlie the arterial alterations that accompany advancing age, novel therapies must emerge that will specifically target these pathways, and retard or reverse "unsuccessful" arterial aging. The substantial variability among older persons in the degree of arterial stiffening, intimal-medial thickening, and increased pulse pressure also reinforces the possibility of identifying factors that modify them,[1] including lifestyle factors. It is noteworthy that arterial stiffness is inversely related to physical fitness, assessed as maximum oxygen consumption, over a broad age range, and that arterial stiffening is reduced in older individuals who regularly engage in vigorous exercise.[5] Dietary interventions can modulate arterial properties. Food fat content has been shown to adversely affect arterial stiffness and endothelial function; diets that are reduced in sodium are associated with reduced arterial stiffening with aging, independent of their blood pressure lowering effects.[37]

Pharmacologic treatments targeting structural factors have also begun. A novel thiazolium agent that breaks non-enzymatic cross-links reduces arterial stiffness both in non-human primates[38] and in humans.[39] Chronic inhibition of angiotensin receptor signaling also substantially retards the age-associated increase in collagen content and intimal-medial thickening and stiffness in rodents.[11]

Therapies that improve the coupling of ventricular and vascular elastances are likely to improve cardiac function and exercise tolerance in healthy subjects. This concept is supported by two studies in healthy older subjects: Administration of the direct vasodilator sodium nitroprusside caused reductions in reflected waves (manifest as a reduction in preload), resulting in reduced cardiac volumes and higher EF at rest and during maximal exercise as compared with placebo therapy.[40] Administration of intravenous verapamil reduced noninvasive indexes of arterial and ventricular systolic stiffness and improved exercise tolerance and oxygen consumption before reaching anaerobic threshold.[41]

Ischemic Heart Disease

Diagnosis

Although the prevalence and severity of autopsy-documented coronary atherosclerosis show a striking increase with age,[42] the diagnosis may be particularly difficult. This is related to the greater likelihood of silent ischemic disease and of atypical presentations of ischemic disease in the older population.[43] A number of factors may be responsible, including a diminished sensation of chest discomfort and the greater incidence of dyspnea as a manifestation of ischemia, rather than the more usual chest discomfort. These may be due to age-associated changes in myocardial diastolic properties and pericardial compliance. In addition, the ability of older individuals to exercise to the point at which ischemic symptoms occur may be diminished because of the increased likelihood of concomitant diseases.

If it is important to know whether or not an older individual has significant coronary atherosclerosis, it is not sufficient to rely on a negative history alone. The cardiac examination is also of limited value. If the patient can exercise on a treadmill, stress testing may be useful not only to diagnose significant coronary stenoses, but also to detect the presence of exercise-induced arrhythmias, determine the patient's functional capacity, and evaluate the effectiveness of any subsequent therapies. Although specificity tends to decline somewhat as age increases, from 84% in those younger than 40 years to 70% in those over 60 years of age,[44] it is largely reliable, with certain caveats. There is a higher likelihood of baseline ST changes in this population because of the increased incidence of LV hypertrophy and conduction abnormalities, and digitalis intake. In this setting, the predictive accuracy of a positive test is low and a stress test with nuclear imaging is particularly useful. A second caution is that a negative test has a low predictive accuracy when the patient is unable to exercise to 85% to 90% of maximal predicted heart rate. A safe and accurate alternative in patients who cannot exercise sufficiently, or at all, is a pharmacologic test with adenosine, dipyridamole, or dobutamine.[45–47] The accuracy of dipyridamole/thallium-201 scintigraphy is similar in the older and younger populations.[48] Pharmacologic stress echocardiography provides similar sensitivity and improved specificity. Echocardiography also provides information on valve function and any rest or stress-induced abnormalities in regional wall motion. Finally, the predictive accuracy of a test depends not only on the degree of ST segment change, but also on the prevalence of disease in the population being examined. Therefore, there is an increased likelihood of a false-negative stress test in an older population with a high pretest probability of disease. Computer tomographic assessment of the coronary artery calcium score correlates with histologic evidence of coronary calcification and atherosclerotic burden. However, there is a strong age-dependent increase in the score,[49] and its value to rule out disease in individuals with atypical symptoms is less in the older population. The use of cardiac catheterization to diagnose ischemic disease is increasing in the elderly, concomitant with the increasing number and proportion of older individuals who undergo coronary bypass surgery, angioplasty, and valve replacement. Although adverse events themselves are the same, including cerebrovascular and peripheral vascular complications, renal failure, contrast reactions, and disorientation, the incidence of all of these complications is probably higher in older patients.[50]

Management

The principles of angina management are the same in older and younger patients. The search for easily reversible factors may be more rewarding in the elderly, and therefore the possibilities of anemia due to occult malignancy, apathetic hyperthyroidism, hypertension, congestive heart failure, and supraventricular arrhythmias, all of which increase myocar-

dial oxygen demand requirements and decrease supply, should be considered in older patients who present with new-onset or recently progressive anginal symptoms.

The choice of an antiischemic regimen for patients without easily reversible precipitating factors is similar in different age groups. If patients continue to experience significant symptoms despite medical therapy, revascularization should be considered. Aspirin decreases events in older patients with stable angina,[51] although the dose should probably be 81 mg/day because of increased bleeding risks. Beta-blockers significantly improve outcomes in older patients during the postinfarction period.[52] In the older patient, one should determine whether ophthalmologic beta-blockers are also being prescribed, as they may have a systemic effect as well. Despite their proven benefit, however, beta-blockers are often underprescribed in the older population.[53] Although early reports indicated an increased incidence of complications of angioplasty in older individuals, mortality rates for both angioplasty and bypass surgery are decreasing in the elderly.[54,55] Perioperative survival after bypass surgery, however, is decreased in older individuals, primarily because of the increased likelihood of coexisting disease, including diabetes and renal and pulmonary insufficiency, and the increased likelihood of advanced coronary disease and impaired LV function. Age is also an important predictor of adverse cerebral outcomes after bypass surgery, including stroke, encephalopathy, confusion, and deterioration of intellectual function. Nevertheless, long-term survival and pain relief compare favorably with those achieved by medical therapy.

Atherosclerosis is progressive, and an important element in its therapy is to identify and treat factors that predispose to accelerated disease.[56] Studies indicate that treatment of hypertension[57] and smoking cessation[58] decrease the rate of cardiac outcomes in older patients. Over 40% of the older population has insulin resistance as evidenced by the metabolic syndrome. Lifestyle interventions focused on exercise and weight loss decreased the development of diabetes by 71% in the older participants in the Diabetes Prevention Program Study.[59] Primary and secondary treatment of hyperlipidemia with hepatic hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors also improve outcomes in older individuals.[60,61] Although observational studies indicated that estrogen therapy was associated with decreased cardiovascular mortality in postmenopausal women, large-scale randomized intervention studies showed no overall benefit on myocardial infarction or cardiac death.

Acute Myocardial Infarction

Recognition and treatment of acute myocardial infarction are often more difficult in older persons. In this population acute infarction more often presents with CNS symptoms, hypotension, and dyspnea.[61,62] The higher mortality previously reported in older patients with infarction has been confirmed in studies, with a severalfold age-related increase in mortality in the placebo arms of several thrombolytic trials.[63–66] In addition, complications of myocardial infarction, including congestive heart failure (CHF), are also increased in older patients. It is unclear whether these adverse outcomes are related to larger infarcts, more advanced coronary disease, decreased ability of uninfarcted muscle to compensate for the infarcted tissue, or altered healing processes in older individuals. The higher complication rates in older individuals dictate an aggressive approach. Although randomized trials demonstrate a benefit of thrombolytics, when compared to placebo, in the general population, subset analyses demonstrate only nonsignificant trends in the older population. Thus, although the benefits of reperfusion are present, this therapy may also be associated with increased hemorrhagic complications, including intracerebral hemorrhage,[67] and a retrospective analysis from the Comparative Cardiovascular Project demonstrated a survival disadvantage with lytic therapy for those over 75 years of age.[68] The official guidelines of the joint American College of Cardiology/American Heart Association Task Force state that thrombolytic therapy in older individuals is "acceptable" but of "uncertain efficacy."[69]

The disadvantages of thrombolytic therapy are largely overcome with primary angioplasty, and a large review of 23 randomized trials demonstrated reduction in death, nonfatal infarction, and stroke with angioplasty compared with thrombolytic therapy.[70] Although early angioplasty improves outcomes, there is still a marked age effect on mortality and postinfarction complications.[71] One limitation of primary angioplasty is the limited number of hospitals with the necessary facilities and experience to perform the procedure. The Danish Multicenter Randomized study separately reported the results in the subset of those patients over 63 years of age who were randomized to thrombolysis or transfer for angioplasty. The latter group experienced a 46% lower 30-day rate of death, reinfarction, or disabling stroke.[72]

Long-term use of aspirin,[73] beta-blockers[74] and angiotensin-converting enzyme (ACE) inhibitors[75] in the postinfarction period decrease adverse outcomes in older patients, and although utilization is low, it should be part of routine care, if not contraindicated, in this population. Older patients with apical aneurysm formation should probably receive Coumadin. A Netherlands multicenter randomized trial in over 800 patients found that administration of oral anticoagulants resulted in significantly lower incidences of recurrent myocardial infarction and death in patients over 60 years of age.[76] The management of complications, including postinfarction ischemia, LV dysfunction, and frequent and complex ventricular arrhythmias after an infarction, is also similar. Elderly patients with frequent or complex arrhythmias postinfarction or left ventricular dysfunction probably benefit from implantable defibrillators to an extent similar to that of the general population.[77,78]

Hypertension

Hypertension is the most important correctable risk factor for cardiovascular disease in the older population. This is due to both its high prevalence, estimated at up to 40% to 50% in those over 65 years of age, and its significant impact on the development of disease.[79] Convincing evidence for the effectiveness of therapy in those with even mild diastolic arterial pressure elevations,[80,81] as well as in those with isolated systolic hypertension,[82,83] has been demonstrated. In older patients with isolated systolic hypertension, treatment

with a diuretic[84] or a long-acting dihydropyridine calcium antagonist[85] decreased stroke and cardiac event rates.

Initial therapy might be directed to nonpharmacologic maneuvers, including salt and alcohol restriction, weight loss when indicated, and increased physical activity. A randomized trial of reduced sodium intake and weight reduction in those who were obese demonstrated that these benefits were feasible, safe, effective, and additive in elderly hypertensives.[84] There are many agents that can lower blood pressure to a normal value. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) report[85] emphasizes individualization of drug therapy based primarily on the presence of coexisting diseases and endorses long-acting formulations. In the older patient, coexisting coronary disease, diabetes, congestive heart failure, renal impairment, and elevated lipids are more likely to be present. An additional, important, and often coexisting factor is left ventricular hypertrophy, which is often associated with diastolic left ventricular dysfunction. Regression of left ventricular mass in this age group is associated with improved relaxation parameters, without compromising systolic function either at rest or during mild, upright bicycle exercise.[86]

Arrhythmias

There is a significant age-related increase in the incidence and complexity of cardiac arrhythmias.[87,88] This is probably due to age-associated changes in the impulse formation and conduction system that are not related to cardiovascular disease, and also to the well-recognized age-associated increase in mitral annular calcification and in hypertensive, vascular, and ischemic disease. Regardless of etiology, both tachy- and bradycardiac arrhythmias have increased hemodynamic significance in older patients because of the increased dependence on diastolic filling time and the atrial contribution to diastolic filling, as well as a decreased ability of the cardiovascular system to compensate for any arrhythmia-induced stress.

There are minor changes in the resting ECG that can probably be attributed to aging per se. These include a decreased incidence of respiratory sinus arrhythmia, an increase in the PR interval, a leftward shift in the QRS axis, and decreased voltage of the R and T waves. These changes are probably related to decreased parasympathetic tone, fibrosis in the conducting system, and increased distance between the heart and the chest wall. Although there is also an age-related increase in LV hypertrophy, myocardial infarction, and more advanced conducting system disease, these are probably related to the presence of silent or overt cardiac disease.

Ambulatory monitoring is the most valuable and common technique to determine the presence and extent of arrhythmias, their relation to possible cardiac symptoms, and possible adverse prognostic implications. The degree to which an arrhythmia in an older patient is considered abnormal, however, is dependent on the frequency and occurrence of similar arrhythmia in older subjects without disease.

The evaluation of an older patient with suspected arrhythmias should begin with a detailed history concerning the occurrence of palpitations and near-syncopal and syncopal episodes, particularly the onset and termination, relation to medication, food, position, and alcohol, and the degree of hemodynamic compromise. Since the prognostic significance of ventricular arrhythmias is dependent on the presence of underlying cardiac disease, a history of hypertension and of ischemic or failure symptoms should also be obtained. Symptoms compatible with thyroid disease and anemia, not uncommon conditions that often present with cardiac manifestations in the elderly, should also be sought. The ECG remains a useful test for evaluation of an arrhythmia. If the arrhythmia is not present during a 12-lead tracing, long-term monitoring can often be helpful, particularly with the use of loop recorders, which can be worn for extended periods and activated to record the rhythm at the time of the event.

Atrial fibrillation is a common, and probably the most important, arrhythmia in the older age group. The hemodynamic consequences of atrial fibrillation are also more marked in the older population and are due to loss of atrial contribution to LV filling, decreased diastolic time for coronary perfusion, and increased myocardial oxygen demand associated with the higher heart rate. Another significant consequence of atrial fibrillation is the increased likelihood of cerebral and other emboli. The Framingham study investigators[89] reported that the risk of stroke attributed to atrial fibrillation, even after adjusting for the effect of systolic blood pressure, rose from 7.3% in those 60 to 69 years of age to 30.8% in those aged 80 to 89 years. Congestive heart failure within the prior 3 months, hypertension, and previous thromboembolism are each significantly and independently associated with an increased risk for stroke in those over 60 years of age.[90]

The approach to atrial fibrillation includes a search for possible etiologies, and a decision as to whether to pursue a rhythm- versus rate-control strategy and stroke prophylaxis.[91] Evaluation for possible etiologies should include echocardiography to diagnose structural and valve disease, and determine left atrial size, as well as laboratory studies of thyroid function and the presence of anemia. Several studies have compared rate-control and rhythm-control strategies.[91-95] They indicate that rate-control is not inferior to a rhythm control strategy, that maintenance of sinus rhythm is difficult to achieve, and that a rhythm control strategy is associated with increased hospitalization rates. It should be noted that anticoagulation should continue to be pursued, even in patients for whom rhythm control is the goal, and that rate control is defined as a mean heart rate of under 80 beats/minute over a 24-hour period, and not the rate on a single 12-lead ECG.

As noted above, pharmacologic therapy includes anticoagulation for older patients with atrial fibrillation. If a cardioversion strategy is pursued, the antiarrhythmic agent is dependent, in part, on left ventricular function and comorbidities. In the absence of structural heart disease, flecainide, propafenone, and sotalol all have good tolerability and a low incidence of complications. However, ischemic disease is often present in the elderly, and in that setting flecainide and propafenone are relatively contraindicated. Beta-blockers can be used in those with sympathetic-mediated atrial fibrillation. Amiodarone is the most effective agent, but because of side effects it is usually used for those in whom other

therapies have not been successful or in those with left ventricular dysfunction. If amiodarone is used, older patients should be regularly screened for thyroid, pulmonary, and vision abnormalities. The use of catheter ablation for atrial fibrillation has increased and is indicated for patients with significant symptoms who are refractory to pharmacologic therapy.

Bradycardiac arrhythmias are also common in the elderly. In symptomatic patients, it is important to determine whether the symptoms are related to the arrhythmia, since older individuals frequently have several reasons for neurologic symptoms. If long-term ambulatory monitoring demonstrates this relationship, pacemakers that allow proper atrial and ventricular sequencing are particularly useful because of the increased dependence on atrial contribution to LV diastolic filling in the elderly. The impact of single- or dual-chamber pacemaker selection on survival in older patients was reported in a study of 36,312 Medicare patients in the United States.[96] The group was randomly chosen and represented 20% of those receiving pacemakers over a 3-year period. After adjusting for patient and hospital characteristics, both 1- and 2-year survival were significantly better for those patients who received the dual-chamber model.

Congestive Heart Failure

The incidence and prevalence of CHF are significantly increased with age. Approximately 80% of patients hospitalized with heart failure are over the age of 65. Congestive heart failure is now the most common discharge diagnosis for those over 65 years of age, and accounts for over $40 billion in annual expenditures.[97] The high incidence of heart failure is primarily related to the increased likelihood of superimposed ischemic, hypertensive, and degenerative valvular heart disease rather than to myocardial changes associated with aging per se. However, age-related changes in diastolic properties and in the cardiovascular response to β-adrenergic stimulation may result in increased or altered symptomatology in the face of any given stress.

The pharmacologic agents used for the treatment of CHF in older individuals are the same as the ones used to treat middle-aged and younger patients, and include diuretics, ACE inhibitors, beta-blockers, and digitalis. In the enalapril trial of patients in severe heart failure, the average ages of the placebo and the treatment groups were 70 and 71 years, respectively.[98] Enalapril therapy was associated with decreased mortality, decreased heart size, and decreased requirement for other medications, as well as with improved New York Heart Association classification. In patients who cannot tolerate ACE inhibitors, the angiotensin receptor blockers should be considered.[99] In the large randomized studies evaluating beta-blocker therapy in patients with heart failure, older individuals tolerated these medications well, and appeared to derive benefits of similar magnitude to younger subjects.[100]

The management of older patients with CHF is complicated by the complex coexisting comorbidities, and the physical and cognitive impairments that afflict older individuals. There is increasing interest in disease management programs, which provide a multidisciplinary approach to the care of a chronic condition such as CHF. These programs improve the access of patients to health care, and provide education to patients on warning symptoms and signs of decompensation, and on dietary restrictions and compliance. A number of studies have shown that these disease management programs are effective in reducing the rate of rehospitalization of elderly patients with CHF.[101]

It is important to note that approximately half of older patients with CHF have preserved or slightly reduced systolic function. The prevalence of this entity, often referred to as "diastolic" heart failure,[102] is more common in women than in men, and is usually preceded by a history of hypertension. The symptoms of dyspnea or heart failure result from increased left atrial and pulmonary venous pressures, particularly during exercise. The pathophysiology of this form of heart failure has not been fully elucidated, but includes abnormalities in the diastolic properties of the left ventricle,[103] such as increased left ventricular stiffness and impaired early diastolic relaxation and filling. In addition, patients with heart failure and preserved systolic function have increased aortic stiffness,[104] and the combined arterial and ventricular stiffening during systole results in increased cardiac metabolic demands and decreased left ventricular systolic reserve during stress.[105] There are no specific treatments for patients with diastolic heart failure beyond alleviating myocardial ischemia in patients with coronary artery disease, optimizing blood pressure control in individuals with hypertension, controlling ventricular rate in patients with atrial fibrillation, and relieving pulmonary or peripheral congestion, although recent studies suggest that angiotensin receptor blockers may help reduce the rate of rehospitalization in these patients.[106]

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